Commentary

Title: Modulating Mucins Make Melanin

Linked article: Kim, J. & Choi, H. Br J Dermatol 2021, (Manuscript ID: BJD-2021-1648)

The outermost layer of skin, the epidermis has evolved to provide a physical barrier of protection from harmful substances and invasion of pathogens. The skin barrier consists in part of highly glycosylated proteins called mucins and the epithelium. Epidermal homeostasis is maintained by the proliferation and differentiation of its basal layer keratinocytes that migrate to the superficial layer of the epidermis, and through its regulated inter-cellular communication with the pigment producing cells, the melanocytes. Together, they form a functional unit, the epidermal-melanin unit (EMU) that maintains epidermis integrity and is responsible for skin pigmentation [1].

The work developed by Kim & Choi [2] aimed to correlate the expression levels of mucins with melanogenesis. For this, the authors have found that mucin-like 1 (MUCL1) has a negative correlation with pigmentation level and tyrosinase activity. MUCL1 was first identified as a breast-specific gene due to its most restricted mRNA expression, where it exerts an important role in breast cancer cell proliferation [3, 4]. Its limited expression in normal breast tissue makes MUCL1 an attractive tumor-associated antigen for targeted therapy of breast cancers. Significant mRNA expression levels of MUCL1 were previously reported in skin [4] but Kim & Choi further show that MUCL1 expression in melanocytes regulates the melanogenic pathway. They also clearly demonstrate that the effect of MUCL1 silencing in melanin biosynthesis can be rescued by the addition of the essential amino-acid threonine, which constitutes a particularly interesting finding.

Melanin derives from the amino acid L-tyrosine, involving the action of at least three key melanogenic enzymes, tyrosinase, and tyrosinase-related proteins-1 and -2 [5] and several amino acids, peptides and their analogs have been described to participate in the fine-tuning pigmentation in the skin [6]. As interesting observations were described by Kim & Choi, additional questions should now be addressed, to clarify if threonine inhibits tyrosinase activity directly or affects pigmentation by increasing MUCL1 levels. These studies can be used to develop new peptide-based drugs to control skin pigmentary disorders.

Additionally, mucins comprise a family of glycoproteins with diverse functions, establishing not only a mechanical barrier to pathogens, but also controlling proliferation and migration of epithelial cells [3,4]. While mucins have been studied in other organs, their role in skin has received less attention. Importantly, mucins overexpression has been observed in several cutaneous malignancies [7], such as the rare primary mucinous carcinoma of the skin [8] and in primary non-metastatic melanomas [9]. It will be of interest to study into more detail the expression of MUCL1 in melanoma cells, as Kim & Choi have established a first correlation between threonine supplementation to recover MUCL1 expression levels in a heavily pigmented melanoma cell line, derived from a metastasis. Melanomas are very heterogeneous skin tumors resulting from the malignant transformation of melanocytes, and it has been observed that melanin presence in metastatic melanoma cells decreases the effect of radiotherapy [10]. It will be of interest to further analyze MCUL1 expression profile in melanomas and address the possible implications of MUCL1 regulation in the outcome of cutaneous skin tumor therapy.

To conclude, the studies developed by Kim & Choi raise interesting observations for the pigmentation field, pointing to the need future studies to explore the role of mucins in the control of melanin synthesis and distribution, with implications for a variety of skin conditions.

Cristina Casalou[1] https://orcid.org/0000-0003-3198-2783
Desmond J Tobin[1,2] https://orcid.org/0000-0003-4566-9392

[1]The Charles Institute of Dermatology, School of Medicine, University College Dublin, D04 V1W8 Dublin, Ireland.
[2]The Conway Institute of Biomolecular and Biomedical Research, University College Dublin, D04 V1W8 Dublin, Ireland.

References

1- Weiner, L, Fu, W, Chirico, W and Brissette, J. Pigment Cell Melanoma Res. Skin as a living coloring book: how epithelial cells create patterns of pigmentation. 2014, 27, 1014-1031.
2- Kim, J. & Choi, H. Br J Dermatol 2021. *In press*
3- Colpitts TL, Billing, P, Granados, E, Hayden, M, Hodges, S, Roberts, L, Russel, J, Friedman P and Stroupe, S. Tumor biology. Identification and immunohistochemical

characterization of a mucin-like glycoprotein expressed in early-stage breast carcinoma. 2002, 23, 263-278.
4- Conley, SJ, Bosco, EE, Tice, DA, Hollingsworth, RE, Herbst, R and Xiao, Z. Oncogene. HER2 drives mucin-like 1 to control proliferation in breast cancer cells. 2016, 35, 4225-4234.
5- Tobin DJ. Pigmentation and Photoaging, Book Chapter 6, *in* Cutaneous photoaging. Ed Watson, R and Griffiths, 2019.
6- Boo, YC. Biomedicines. Up- or Downregulation of Melanin Synthesis Using Amino Acids, Peptides, and Their Analogs. 2021, 8, 322.
7- Chakraborty, S, Bonthu, N, Swanson, BJ and Batra, SK. Cancer Lett., Role of Mucins in the Skin benign and malignant conditions. 2011, 301, 127-141.
8- Karimipour, Dj, Johnson, TM, Kang, SK and Lowe, L. Journal Am. Acad. Dermatol, Mucinous carcinoma of the skin. 1997, 36, 323-326.
9- Riker, AI, Enkemann, SA, Fodstad, O, Liu, S, Ren, S, Morris, C, Xi, Y, Howell, P, Metge, B, Samant, RS, Shevde, L, Li, W, Eschrich, S, Daud, A, Ju, J and Matta, J. BMC. Med. Genomics. The gene expression profiles of primary and metastatic melanoma yields a transition point of tumor progression and metastasis. 2008, 8, 1-13.
10- Broznya, AA, Józwichi, W, Roszkowski, Fillipiak, J and Slominski, AT. Oncotarget. Melanin content in melanoma metastases affects the outcome of radiotherapy. 2016, 7, 17844-17853.